REMARKS/ARGUMENTS

I. Status of the claims

Claims 35, 37, 40-45, 47-49, and 57 are amended. Claims 59-63 are added. With the entry of this amendment, claims 35-63 are pending.

II. Support for the amendments

Support for the amended claims can be found in the specification, drawings and originally-filed claims. For example, support for the amendments to claim 35 represent the nucleotides in SEQ ID NOs: 16 and 17 that are displayed in Figure 18(b). Support for the amendments to claim 40 can be found, e.g., in Table 1 on page 60 of the specification. Support for "9500" in claim 47 can be found in the specification on, e.g., page 32, lines 10-14 of the specification. New claims 59-62 merely separate out subject matter recited in their respective independent claims. Support for new claims 63 can be found in original claims 1 and 2. No new matter is added.

III. Drawings

The Examiner indicated that Figure 25 was not supplied in the formal drawings submitted in 2002. Applicants' records indicate otherwise. However, to expedite prosecution, a new formal drawing of Figure 25 is submitted with this Amendment.

IV. Claim objection

The Examiner objected to claim 35 because it referred to sequences in a figure rather than to a SEQ ID NO. As amended, the claim refers to nucleotides in SEQ ID NOs: 16 or 17 that correspond to the sequences depicted in Figure 18(b). Accordingly, Applicants respectfully request withdrawal of the objection.

V. Rejection under 35 U.S.C. § 101

The Examiner rejected claims 45 and 57 as allegedly encompassing non-statutory subject matter (i.e., transgenic humans). As amended, claims 45 and 57 are directed to isolated cells. Accordingly, the claims do not encompass transgenic humans. Withdrawal of the rejection is requested.

VI. Rejection under 35 U.S.C. § 112, first paragraph: written description

The Examiner rejected claims 35-58 as allegedly not complying with the written description requirement. Applicants respectfully traverse the rejection.

Regarding claim 35, while the Examiner appeared to acknowledge that the specific sequences recited in the claim are taught in the specification, he argued that those of skill in the art "would not be able to predict that ... [the claimed human fragment] ... would function the same as that of the rat." *See*, Office Action, page 8. The Examiner acknowledged that the rat sequences did comply with the written description requirement.

The written description requirement, as the Examiner correctly acknowledges, requires that the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *See*, Office Action, page 5. The Written Description Guidelines state: "The written description requirement for a claimed genus may be satisfied through sufficient description of ... identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure..." (emphasis added). *See*, Office Action page 7.

Applicants dispute the relevance of the Examiner's reference to the *Fiers v. Revel and The Regents of the University of California v. Eli Lilly Co.* cases in regard to the present application. Both *Fiers* and *Eli Lilly* were directed to applications that claimed DNA sequences that were not yet cloned and could not be readily identified. In contrast, the present application provides the exact sequences at issue. Since the Examiner's concerns seem to be focused on whether the claimed sequences actually work, it appears that the Examiner's concerns are more properly a question of enablement, not description. Thus, Applicants question the propriety of

the rejection, given that the sequences recited in the claims are specifically recited in the application.

The present specification provides the exact sequences of the enhancer sequences encompassed by the claims (*see, e.g.*, Figure 18(b)) as well as a description of standard molecular biology methods for their isolation. Moreover, the application provides sufficient information to teach those of skill in the art the functional characteristics of the claimed promoters as well as a correlation between specific CArG elements and gene expression. This is exemplified in the application, which teaches, *inter alia*, that:

1. the full-length rat and human sequence function in an equivalent manner in mice (*see, e.g.*, Figures 9 and 10 and page 8, lines 17-25, stating in part: "Results show that the human promoter has activity virtually identical to that of the rat SM-MHC promoter.");

2. the recited rat sequence (displayed in Figure 18b), when linked to a basal promoter results in smooth muscle cell expression in mice (*see, e.g.*, Table 1 on page 60);

3. CArG elements in the rat sequence play a functional role in the rat promoter/enhancer (*see, e.g.*, page 58, line 24 to page 59, line 21); and

4. an alignment of the rat and human promoter/enhancers identifying their common sequences, including common CArG elements previously demonstrated to have a functional role in the rat sequence (*see, e.g.*, Figure 18b).

Based on this data, those of skill in the art would have recognized that Applicants were indeed in possession of the invention claimed in claim 35, including a promoter/enhancer comprising the recited human sequence (nucleotides 6862-7100 of SEQ ID NO:17). Given that the human and rat full length promoter/enhancers have equivalent activity and a clear correlation of structure between the rat and human promoter/enhancers as well as functional data from the rat sequence, those of skill in the art would have understood that applicants were in possession of the claimed invention as of the filing date. Indeed, the data provided in the patent application provides detailed promoter/enhancer analysis of the rat promoter allowing for accurate prediction of the elements of the rat sequence responsible for function. Since the human sequence has the same functional effect when introduced into mice and has an analogous structure to the rat sequence, Applicants have set forth sufficient information in the patent application to fully

describe the subject matter of claim 35. It is irrelevant if there is some variation in sequence between the rat and human sequences when the full promoter/enhancers have the same expression and the same relevant structural elements (CArG elements) with known correlation to function.

Regarding claim 40, the Examiner argued that only claims reciting specific sequence mutations, and reciting that the promoter was or was not expressed in specific tissues, and only limited to the rat sequences complied with the written description requirement. Similarly, with reference to claim 47, the Examiner argued that claims reciting only specific sequences (1-6700 and 11,700-13,700 or 1-6700 and 11,700 to 15,800) and specific organ expression were properly described.

Applicants submit that it is unreasonable to limit Applicants to the exact mutation of the CArG elements used in the example rather than to any mutation as recited in the claims because the mutations effecting CArG element binding of transcription factor could be readily identified. In fact, CArG elements were well known cis-acting elements of promoters and enhancers and in fact had been well studied in the context of smooth muscle cell promoters. As explained in Miano, *J. Mol. Cell. Cardiol.* 35:577-593 (2003) (Exhibit A), a large number of promoters containing identified CArG elements were known as of the filing date. Indeed, Miano states that at least 60 such sequences were known in early 2003. Thus, those of skill in the art would have readily understood the CArG element consensus (CCXXXXXXGG, where X is typically selected from A and T). Therefore, those of skill in the art could have readily determined which sequences would eliminate transcription factor binding. Applicants acknowledge that the Miano reference was published approximately one year after the filing date of the present application, but submit that it is a review article summarizing the art as of the filing date. *See, e.g.*, Miano, Table 1, referencing a large number of promoters comprising CArG elements published on or before 2002.

With reference to the specific tissues in which the promoter/enhancers recited in claims 40 and 47 act, Applicants have amended the claims as the Examiner requested to recite that the promoters initiate or do not initiate expression in the tissues described in the

specification. Applicants note that the claims do not specify whether or not expression occurs in other tissues.

In view of the comments above, Applicants respectfully request withdrawal of the rejections.

VII. Rejection under 35 U.S.C. § 112, first paragraph: enablement

The Examiner also rejected claims 35-58 as allegedly not enabled across their full scope. Specifically, the Examiner argued that SMC gene expression was complex and that there was divergence in the number of CArG elements between rat and human sequences, apparently attempting to question whether it was reasonable to extrapolate results from the rat to the human MHC promoters. *See*, Office Action, pages 14-16. The Examiner also argued that there was not sufficient teaching to enable initiation of expression in any animal or to predict the effect of other CArG elements. *See*, Office Action, page 17. Applicants respectfully traverse the rejection.

To establish a *prima facie* case of non-enablement, the Examiner must show that undue experimentation would be required to make and use the claimed invention. Even if the practice of the claimed invention requires a considerable amount of experimentation, it is not necessarily "undue" experimentation:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or it the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) (citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976).
> MPEP § 2164.06.

The present claims are enabled because those of skill in the art could have made and used the full scope of the claimed compositions without undue experimentation.

With regard to the references the Examiner cites on pages 14-16 of the Office Action, Applicants submit that they are not sufficient to prove non-enablement of the claims. The Manabe *et al* reference, which provides at least some of the data provided in the present application, is only quoted from its introduction, i.e., describing the prior art before the inventors'

data about MHC was known. The reference is also cited as stating that no single regulatory region or enhancer controls the entire temporal or spatial regulation of MHC. While this may be true, it is irrelevant to enablement of the claims. The claims do not recite that the claimed fragments control every temporal or spatial regulation of MHC. The claims at most state that the recited control elements initiate expression in a smooth muscle cell *in vivo*. Indeed, the specification details how there are different control elements in the MHC promoter/enhancer that regulate different subsets of smooth muscle cells expression.

The Forsythe *et al.* reference cited by the Examiner, if anything, appears to support enablement of the claims. The Examiner cites the reference as allegedly disclosing that the human promoter/enhancer contains at least one more CArG element than the rat promoter/enhancer. The abstract does not mention the rat sequence at all and makes no comments regarding a different number of CArG elements between the two species. In fact, the abstract states that the human intronic region of MHC was isolated and two CArG elements were identified. One, based on location ("+1970"), appears to correspond to the intronic CArG element described in the present specification. The other is much farther downstream and is not specifically identified in either the rat or human sequences in the patent application. Thus, there is no basis for the Examiner to argue that the number of CArG elements differ between rat and human MHC promoter/enhancers.

Significantly, Forythe *et al.* clones each of the intronic CArG sequences they identified and operably linked them to a basal promoter and reporter sequence. As would be predicted from the present specification, insertion of the intronic CArG elements led to increased expression in at least one smooth muscle cell line. Indeed, for the CArG element corresponding to the one encompassed by claim 35, Forsythe found higher expression in both tracheal and vascular smooth muscle cell lines. Thus, if anything, Forsythe provides data consistent with the present claims.

The Examiner also questioned whether those of skill would be able to obtain a polynucleotide capable of directing expression in any animal. Applicants submit that the data in the specification provides strong evidence for the interchangeablility of SMC promoters across species. Specifically, the application teaches that either the human or rat promoter/enhancers

provide smooth muscle cell-specific expression in mice. Thus, three different animals appear to recognize the same transcriptional motifs. To the extent the Examiner may believe that a *prima facie* enablement rejection was raised base don this issue, Applicants submit that the data provided in the specification rebuts the rejection.

The Examiner also questioned whether subsets of SMCs other than those actually reduced to practice are enabled. While Applicants assert that those of skill in the art could indeed achieve other subsets of expression without undue experimentation, to expedite prosecution, Applicants have indicated that the promoter/enhancers initiate expression in the subsets exemplified in the specification.

Finally, the Examiner questioned whether those of skill could modify CArG elements in ways other than the way disclosed in the application. As discussed above, CArG elements were well known cis-acting elements of promoters and enhancers and in fact had been well studied in the context of smooth muscle cell promoters. As explained in Miano, *J. Mol. Cell. Cardiol.* 35:577-593 (2003)(Exhibit A), a large number of promoters containing identified CArG elements were known as of the filing date. Indeed, Miano states that at least 60 such sequences were known in early 2003. Thus, those of skill in the art would have readily understood the CArG element consensus (CCXXXXXXGG, where X is typically selected from A and T). Therefore, those of skill in the art could have readily determined which sequences would eliminate transcription factor binding without undue experimentation.

In view of the above remarks, Applicants respectfully request withdrawal of the rejections.

VIII. Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claim 43 as indefinite for not providing a definite article. Applicants thank the Examiner for noting this error. As amended, the claims include the definite article "the" to indicate that the promoter of claim 40 is intended.

Claim 44 was rejected for depending from the improper claim, thereby creating an antecedent basis problem. As amended, claim 44 depends from claim 43 as suggested by the Examiner.

The Examiner argued that claims 47-49 were ambiguous because it was unclear how many nucleotides could be deleted in the "intervening" nucleotides. Applicants have amended the claims as suggested by the Examiner.

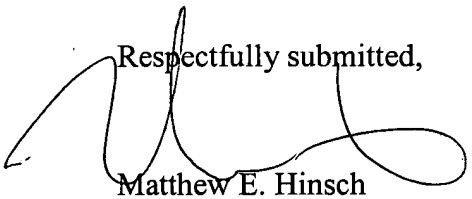
Accordingly, Applicants respectfully request withdrawal of the rejections.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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